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10/627,331	07/25/2003	Arthur M. Krieg	C1039.70078US00	4362

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EXAMINER	
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ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,331	KRIEG ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50, 52-53, 55-57, 59-60, 62-64, 66-70, 72-86 and 97-102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50,52,53,55-57,59,60,62-64,66-70,72-86 and 97-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/17/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/02/2007 has been entered.

2. This office action is to take the place of the action mailed on 02/25/2008. Applicant should disregard the 02/25/2008 action for it is vacated.

Status of Claims

3. Claims 1-49, 51, 54, 58, 61, 65, 71 and 87-96 are cancelled. Claims 97-102 are added. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70, 72-86 and 97-102 are under examination.

Claim Rejections - 35 USC § 112

4. The written description rejection is withdrawn in view of Applicant's submission.

5. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70, 72-86 and 97-102 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to the enablement rejection, Applicant argues that the claimed invention is enabling because the CpG oligonucleotides induce a pattern of immunostimulation that is consistent with viral infection. To substantiate Applicant's arguments, Applicant notes that Applicant have demonstrated in the specification, via working examples, that the oligonucleotides stimulate B cells, natural killer cells and monocytic cells; and production of interferon-gamma, increases the number of spleen cells secrete IL-6, IL-12, IFN-gamma, IFN-alpha, IFN-beta, IL-1, IL-3, IL-10, TNF-alpha, TNF-beta, GM-CSF, RANTES; and that an increased in IL-6 expression was found to occur in B-cells, CD4+ T cells and monoyctic cells. Applicant also argues that the contrary to the Office's assertion, use of CpG ODN across species is predictable.

Applicant's arguments have been considered, however, it not found persuasive. The Office acknowledges the immunostimulatory effects of oligonucleotides containing CpG motifs, however, the issue here is that Applicant has not taught or shown the skilled artisan in the art how to harness the immunostimulatory activities to render it therapeutic in the manner relating to the claimed invention. There is a difference in showing immunostimulatory activities and showing a therapeutic efficacy. As provided in the previous office actions, it is known in the art that these oligonucleotides induce a Th1 biased immune response, which produces Th1 associated cytokines, and that the induction of a Th1 immune response is also important to resolving infections. However, the art that a balance between a Th1 and Th2 immune response is of importance in resolving infection, see teachings of Infante-Duarte et al. In the instant case, it is noted that Applicant has not set forth any guidance relating to the maintenance of a Th2

immune response. It appears that Applicant is concerned with is the stimulation of a Th1 biased immune response, yet, Applicant has failed to set forth any guidance as to the type and level of immune profile that the oligonucleotides must ascertain in order to render it therapeutically effective. As mentioned, Applicant has not taught the skilled artisan how to harness the immunostimulatory activities in the manner that is consistent with the claimed invention. What is the level of B cell, natural killer cells, monocytic cells, IFN-gamma, IL-6, IL-12, IFN-alpha, IFN-beta, IL-1, IL-3, IL-10, TNF-alpha, TNF-beta, GM-CSF, RANTES; IL-6 expression in B-cells, CD4+ T cells and monoyctic cells necessary to treat, prevent and ameliorate HBV infection? Are any of the oligonucleotides taught the specification capable of such activities? As noted in the previous office action, Krieg et al. (Krieg et al. CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760.) advised that each oligonucleotides are distinct from one another for each has a different immune profile. Thus, what is the immune profile required to treat, prevent and ameliorate HBV infection? And what is the sequence of the oligonucleotide that is capable of inducing the required immune profile? In the instant case, Applicant has not provided any answer or guidance to relating to these questions. In the absence of such, Applicant's claimed invention is merely an invitation to experiment. The skilled artisan would have to blindly experiment with every variable encompassed by the claimed invention. And the imposition of blind experimentation would necessarily result in the burden of undue experimentation. Applicant has provided an allegation of enablement based on the ability of the CpG oligonucleotide to induce a Th1 biased immune response. Yet,

Applicant has failed to demonstrate anything that commensurate in scope with the claimed invention. The claimed invention is not solely directed at immune stimulation. Instead, the claimed invention is directed at treating, prevent and ameliorating the infection. Hence, while Applicant arguments have been considered, it is not sufficient to overcome the rejection. It should further be noted that in the years following Applicant's filing of the claimed invention, the art still has not recognize the use of CpG oligonucleotides as an active ingredient in treating, preventing and ameliorating HBV infection. At the very most, the art acknowledges the use of these oligonucleotides as an adjuvant in vaccines. See the teachings of Krieg et al., (Krieg et al. Antiinfective Applications of Toll-Like Receptor 9 Agonists. Proc. Am. Thorac. Soc., Vol. 4, 2007, 289-294.) particularly page 291.

Regarding Applicant's assertion that the use of CpG OND across species is predictable, Applicant is reminded that arguments cannot take the place of evidence. Applicant has not provided any data or evidence supporting Applicant's assertion. Meanwhile, the Office has clearly set forth its position of unpredictability. The Office directs Applicant's attention to Table 1 of Mutwiri et al. Table 1 clearly evidence that the type and quality of immune stimulation induced by CpG oligonucleotides are unpredictable across species. And, it should be noted here that the breadth of the claims is not limited to just humans and mice. Rather, as indicated in the enablement rejection, the breadth of the claims is directed to encompass human or vertebrate animal including a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat, and mouse.

Additionally, it is noted that Applicant argues that the Office has failed to establish a prima facie case of lack of enablement because the only doubts raised by the Office about the enabling nature of claimed invention is related to the lack of predictability and lack of an in vivo test of viral infection. This argument has been considered, however, it is not found persuasive. Contrary to Applicant's assertion, the Office has clearly established a prima facie case of lack of enablement. In the enablement analysis, the Office clearly followed the Wands factors, the factors used in determining enablement or lack thereof. Applicant is also reminded that the enablement rejection is not made solely on the lack of an *in vivo* test for viral infection. Rather, the enablement rejection, again, is based on the Wands factors as a whole. In the instant case, the absence of an *in vivo* data does not further advance Applicant's assertion of enablement. Moreover, it should be noted that Applicant has not even provided an *in vitro* data demonstrating or evidencing that the CpG oligonucleotides, by itself, reduce viral load.

It is further noted that Applicant argues that the administration of cytokines are different from administering a natural component that induces the body to produce a balanced immune response. Applicant argues that a single cytokine may bring to a benefits but it may throw off the balance of other factors leading to problems and side effects. Applicant asserts that the issues of enablement for a CpG oligonucleotide and a cytokine are not the same.

Applicant's arguments have been considered, however, it is not found persuasive. While the issues of enablement for a CpG oligonucleotide and a cytokine

are not the same, the issues remain similar. As Applicant asserted, a single cytokine may bring benefits and throw off the balance of other factors leading to problems and side effects. This exact issue remains to be addressed CpG oligonucleotides. In the instant case, the induction of a Th1 biased immune response by these oligonucleotides would necessarily "throw off the balance of other factors leading to problems and side effects". Such factors include Th2 immune response, which is also required for the resolution of infection, as noted by Infante-Duarte et al. As noted throughout this office action, Applicant is reminded that arguments cannot take the place of evidence. If Applicant's claimed invention is enabling as Applicant alleges, the Office invites Applicant to submit data that commensurate in scope with the claimed invention.

It is further noted that Applicant has reiterates Applicant's previous arguments. The following is directed at those arguments.

As previously noted, in response to the enablement rejection, Applicant argues that the claimed invention is enabling. To support Applicant's arguments, Applicant argues that he specification contains working examples to show the production of antibody in response to oligonucleotide stimulation, stimulation of B cells, natural killer cells and monocytic cells, and production of IFN-gamma and other cytokines. [Examples 2-4, 11, Figures 6, 11 and 15.] Applicant notes that the specification asserts that CpG oligonucleotides are useful in treating viral infections including hepatitis B viral infection. Applicant further notes that Applicant has provided sufficient direction and guidance in the specification to enable the skilled artisan to practice the claimed invention. Applicant also notes that Applicant have provided preferred modes of

administration and formulations. Applicant also disagrees with the Office's position of unpredictability and quantity of experimentation necessary.

Applicant's arguments has been considered, however it is not found persuasive. The Office acknowledges the working examples disclosed in the specification. It is further noted that from this immunostimulatory observation, Applicant asserts that the oligonucleotides are useful in treating various diseases, including hepatitis B viral infection. However, as Applicant has noted, all that the Office has found is an "assertion" of use rather than any guidance or direction that would enable the skilled artisan to practice the claimed invention without the burden of undue experimentation. In the instant case, Applicant has not disclosed of a single oligonucleotide encompassed by the claimed invention to be therapeutically effective for HBV. Nor has Applicant sets forth an immune profile that the oligonucleotide must provide to render it therapeutically effective in HBV treatment. In the instant case, as noted by Applicant, all Applicant has taught is that the oligonucleotides are immunostimulatory. From this observation, Applicant associated the immunostimulatory activities to treating HBV. However, the association is not substantiated by any evidence demonstrating that the oligonucleotides are therapeutically effective for HBV. There is no *in vitro* nor *in vivo* model presented in the speciation to evidence that oligonucleotides encompassed by the claimed invention are therapeutic. In the instant case, Applicant has failed to set forth any guidance that would enable the skilled artisan to harness the observe immunostimulatory activity to render a therapeutically effective HBV treatment. As noted previously, nothing exists in the specification demonstrating that the fundamental

research necessary for the claimed invention has been conducted to support Applicant's assertion of therapeutic efficacy for the oligonucleotides.

While it is noted that a portion of the specification is dedicated to modes of administration and preferred formulation, however, it should be noted that the enablement rejection is not directed at how to administer or formulate the oligonucleotides. The enablement rejection is directed at the failure of the specification to enable the skilled artisan to practice the claimed invention without the burden of undue experimentation. In the instant case, as noted above, Applicant has not evidence that an oligonucleotide is therapeutically effective in HBV treatment.

It is further noted that Applicant objected to the Office conclusion that all that is present in the specification are conjectures of potential application of such oligonucleotides against viral infection, and requested the Office to substantiate this position.

Applicant's objection has been noted, however, the Office stands by this position. In this case, Applicant has not shown or taught that an oligonucleotide comprising the CpG motif has a therapeutic affect against viral infection. All that Applicant has shown is that these oligonucleotides are immunostimulatory, and from these immunostimulatory activities, Applicant asserts that they are useful in the treatment of viral infections. Applicant has not substantiated this assertion by any facts that correlates and commensurate with the claimed invention. As mentioned, the claimed invention is specifically directed at treating, preventing and ameliorating HBV infection. However, Applicant has not taught or provided any guidance directing at the type of

immunoparameter that must be modulated, which oligonucleotide has this immunomodulatory activity, and the extent in which the modulation must occur to render a therapeutic effect against HBV infection. All that is present is an assertion of use without any substantiating evidence. Similarly, all that is present are conjectures, reasoning that involve the formation of conclusions from incomplete evidence, of use.

Applicant further submits that much of the art cited in the enablement are not relevant to the current claimed invention. Applicant also asserts that there is no evidence of unpredictability of the invention.

Applicant's submission has been considered, however, it is not found persuasive. It should be noted that the claimed invention is directed at the treatment of HBV infection with the administration of a CpG oligonucleotide. The claimed invention is directed at the administration of CpG oligonucleotides to stimulate a Th1 immune response, which induces the production of Th1 associated cytokines. In the instant case, while the claimed invention does not specifically recite the administration of a cytokine, it does rely on the production of a Th1 associated cytokines to render a therapeutic efficacy for a disease. Hence, the cytokine art was introduced in the enablement rejection to demonstrate the level of unpredictability and the quantity of experimentation that would be required of the skilled artisan attempting to practice the claimed invention. In the instant case, the Office relies on the cytokine art to establish that the skilled artisan would not be able to practice the claimed invention without an undue burden of experimentation.

Additionally, these post-filing art evidences that a method of treating HBV with the administration of an oligonucleotide comprising the CpG motif has not been ascertained by any skilled artisan in the relevant art.

It is further noted that Applicant criticizes the Office for citing teachings of the cytokine art. Applicant argues that it is not clear how the teachings are relevant to the claimed invention, which is directed at method of treatment for HBV with the administration of oligonucleotides.

Applicant's criticisms have been noted, however, because Applicant has disclosed in the specification that the claimed invention relies on the immunostimulatory activities of oligonucleotides comprising CpG motifs to treat HBV. Specifically, Applicant disclosure suggests taking advantage of the Th1 biased immune response induced by the oligonucleotides to treat HBV. In association with a Th1 immune response is the induction of Th1 associated cytokine profiles. The induction of Th1 associated cytokines necessarily follows the production of a Th1 immune response. Hence, the Office cited the teachings of the cytokine arts. These teachings demonstrated that the direct administration of cytokines itself is unpredictable. Hence, if the direct administration of cytokines is unpredictable, it logically follows that the indirect administration of cytokines, via stimulation of a Th1 biased immune response, would necessarily be unpredictable, if not more unpredictable.

In addition to above, Applicant criticizes the Office's interpretation of Krieg and Mutwiri et al. Applicant argues that Office conclusion that the absence of TLR9 in some species would lead to variability in results is misplaced, and notes that Mutwiri et al.

discloses that in vitro stimulation of cells by CpG motifs is conserved across species. In response to the Office position that every oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies…etc.," Applicant argues that Applicant has described a class of oligonucleotides comprising the CpG motif that favors a Th1 immune response, and that variability in the immune response induced by the oligonucleotides should not be the cause for a lack of enablement. Applicant further argues that the statement that the "immunostimulatory activity of CpG oligonucleotides is species specific," does not support a lack of enablement.

Applicant's position has been carefully considered, however, it is not found persuasive. It should be noted that the enablement rejection is not based solely on the species specific immunostimulatory activities nor the variability of the immune response induced by oligonucleotides comprising the CpG motifs. The enablement rejection is made on the basis of the Wands factors. A conclusion of lack of enablement means that claimed subject matter was not described in the specification, in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to use the invention. In this case, the two cited points are directed at the lack of predictability present in the CpG art. The CpG art clearly notes that immunostimulatory activities vary from one species to the next. That is the immunostimulatory activities observed in mice would not necessarily be predictive of the immunostimulatory activities in humans. See Table 1 of Mutwiri et al. The CpG art also clearly cautions that the immune response in each oligonucleotide comprising the CpG

motif is distinct from one another. See Krieg et al. (Krieg et al., CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760.) That is, while Applicant has alleged that Applicant has disclosed a class of oligonucleotides that produces a Th1 biased immune response, however, as noted above, the Th1 associated cytokine profile induced by these oligonucleotides is distinct from one another. The existence of variability in the Th1 associated cytokine profile induced by each oligonucleotides comprising the CpG motif, depending on the length of the sequence, the sequences that flanks the CpG motif, the number of CpG motifs...etc., would not enable the skilled artisan to predictably and routinely pick any oligonucleotide comprising the CpG motif, as encompassed by the claims, to treat HBV. Additionally, it is noted that Applicant has alleged that the Office's conclusion that the absence of TLR9 in some species would lead to variability in results is misplace because Mutwiri et al. discloses that in vitro stimulation of cells by CpG motifs is conserved across species. It appears that Applicant has misconstrued the Office's conclusion. As noted in the previous office action:

- The recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 like proinflammatory cytokines, interferon and chemokines.[1] However, the art also recognizes that TLR-9 is differentially expressed in human mice, and that TLR-9 has

[1] Krieg et al. CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. [Abstract, in particular.]

> not been identified in species other than human and mice.[2] Thus, with the variability of TLR-9 expression, including absence thereof, the level of a Th-1 immune response would also be variable from one species of animals to the next.

The conclusion noted by the Office is the level of Th1 immune response is also dependent on TLR-9 expression, which varies from one species to the next. Moreover, the Office directs Applicant's attention to Krieg et al.[3] Krieg et al. clearly notes that because the cellular patterns of TLR expression varies between different species, the results of TLR stimulation in one species may not be predictive of what will occur in another. Moreover, Mutwiri et al. notes that TLR9 has only been identified in humans and mice. The disclosure of Krieg et al. clearly substantiates the Office's conclusion.

Regarding the teachings of Equils et al., Agrawal et al. and Olbrich et al., Applicant argues that none of the references teaches the claimed invention. Additionally, it appears that Applicant is arguing that the claimed invention is enabling because Olbrich et al. asserts that "If used under the right conditions, CpG-ODN should be a powerful substance for antiviral therapy in the future. Applicant's arguments have been fully considered, however, it is not found persuasive. Had any of these cited references teach the claimed invention, then the issue of enablement would not have been raised. In the instant case, like Applicant, Olbrich et al. does not teach the skilled artisan how to make and use the claimed invention without undue experimentation for

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[2] Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93.]

Olbrich et al. does not teach the skilled artisan how to harness the immunostimulatory activities to render it therapeutic against HBV infection. However, in the instant case, each of the cited references, which published well after the filing date of the claimed invention, evidences that since the discovery of the immunostimulatory activities of CpG oligonucleotides, the art failed to harness the activities to render it therapeutic against viral infection. Like other arts cited, the references were cited to demonstrate that a high level of unpredictability exists.

While all of Applicant's arguments and criticisms have been carefully considered, the entire submission is not sufficient to overcome the enablement rejection. In this case, Applicant has failed to evidence that the claimed subject matter was described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

In all, Applicant is reminded that the enablement rejection is made on the basis of the Wands factors. In view of the Wands factors, as established in the previous office action, it is found that the specification is not enabling for the claimed invention. While Applicant may argue that the specification is enabling, the evidence as a whole evidences that Applicant has enabled the skilled artisan to practice the claimed invention without undue experimentation. Applicant has not provided a single working example that is directed at demonstrating at an oligonucleotide comprising the CpG motif is therapeutic against HBV infection, nor any guidance evidencing that said oligonucleotide is indeed therapeutic against HBV infection. This is further exemplified

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[3] Krieg et al. Antiinfective Applications of Toll-Like Receptor 9 Agonists. Proc. Am. Thorac. Soc., Vol. 4,

by Applicant's submission, wherein Applicant repeatedly asserted that Applicant teaches the use of the oligonucleotide to induce an immune response. And, Applicant is reminded that this teaching does not commensurate in scope with the claimed invention.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Breadth of the claims:

The claimed method of treating, preventing or ameliorating hepatitis B viral infection in a subject with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to the subject.

2007, 289-294.

The specification provides the following,

A "subject" shall mean a human or vertebrate animal including a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat, and mouse. [Lines 31-32, page 19.]

Hence, the breadth of the claims is directed to a method of treating, preventing or ameliorating hepatitis B viral infection in a subject with the administration of an oligonucleotide comprising at least one unmethylated CpG motif to the subject. The subjects encompassed by the claimed invention are all vertebrate animals, including humans.

Presence or Absence of working examples:

The specification does not contain any working examples that are directed to the claimed invention, a method of treating, preventing or ameliorating hepatitis B viral infection in a subject with the administration of an oligonucleotide comprising the CpG motif. The specification does not containing any working examples demonstrating that such oligonucleotides treat, prevent or ameliorate hepatitis B viral infection. Nothing exists in the specification demonstrating that fundamental research has been conducted to support Applicant's claim, wherein oligonucleotides comprising the CpG motif treat, prevent or ameliorate hepatitis B viral infection in vertebrate subjects.

Amount of direction or guidance present in the specification:

The specification does not contain any evidence demonstrating that oligonucleotides containing the CpG motif treat, prevent or ameliorate hepatitis B viral infection in vertebrate subjects. All that is present in the specification are conjectures of

potential application of such oligonucleotides in the treatment, prevention and amelioration of viral infections in vertebrate subjects.

Nature of the invention

Based on Applicant's disclosure, it appears that the nature of the claimed invention is directed to the use of the immunostimulatory activity of oligonucleotides containing the CpG motif, including the induction of Th1 immune response invoked by the production of Th1 associated cytokines accorded by the CpG motif to render a therapeutic value, wherein the desired therapeutic value is to provide treatment, prevention and amelioration of hepatitis B viral infection in vertebrate subject--immunotherapy.

State of the Art:

In the instant, the involvement of a Th1 type immune response in combating against intracellular pathogens is a well-recognized general concept. The art acknowledges the importance of Th1 type immune response, which is stimulated by the production of Th1 associated cytokines, in the elimination of intracellular pathogens, including viruses. However, the art has not accredited or recognized any one particular Th1-associated cytokine to the treatment, prevention and amelioration of viral infection in a subject. Specifically, the art teaches that while cytokines secreted by T helper cells are of critical importance for the outcome of many infectious diseases, the production of the "right" set of cytokines can be a matter of life or death, as noted by Infante-Duarte et al. Infante-Duarte et al. further notes that in addition to a Th1 type immune response, a Th2 type immune response is also necessary. Specifically, Infante-Duarte et al.

teaches that a tight control over where and when Th1 and Th2 immune responses happen is necessary to keep intracellular infections under control, and to prevent the Th1 type immune response from causing damage to the host.[4] Hence, while the importance of a Th1 type immune response is well recognized in the art, the art further notes that a balance between Th1 and Th2 type immune responses is necessary to resolve an infection.

The cytokine art also provides that the efficacy of Th1 associated cytokines, such as interleukin 2, interleukin 12 and interleukin 18, against intracellular pathogens are controversial, as evidenced by Aoki et al.,[5] Bohn et al.,[6] Sakao et al., [7] Zaitseva et al., [8] and Masihi, K. [9] Aoki et al. teaches that while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent *M. bovis* infection. Bohn et al. teaches that interleukin-12, a Th1 associated cytokine, induces different effector mechanisms that result in either protection or exacerbation of a disease. Specifically, Bohn et al. notes that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice. Sakao et al. teaches that interleukin 18, a Th1 associated cytokine, is

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[4] Infante-Duarte et al., Th1/Th2 balance in infection. Springer Seminars in Immunopathology, 1999, 21: 317-338. [Paragraph bridging pages 321-322, in particular.]
[5] Aoki et al. Use of cytokines in infection. Expert Opin. Emerg. Drugs, 2004, vol. 9, No. 2, 223-236. [Lines 4-15, left column, page 229,in particular]
[6] Bohn et al., Ambiguous role of interleukin-12 in Yersinia enterocolitica infection in susceptible and resistant mouse strains. Infect. Immune., 1998, Vol. 66, 2213-2220. [Abstract, in particular.]
[7] Sakao et al. IL-18-deficient mice are resistant to endotoxin-induced liver injury but highly susceptible to endotoxin shock. Int. Immunol., 1999, Vol. 11, 471-480. [Abstract, in particular.]
[8] Zaitseva et al. Interferon gamma and interleukin 6 modulate the susceptibility of macrophages to human immunodeficiency virus type 1 infection. Blood, 2000, Vol. 96, 3109-3117. [Abstract, in particular]

responsible for the progression of endotoxin-induced liver injury in mice primed with interleukin 18. Zaitseva et al. teaches that both interleukin 6 and interferon gamma augment the susceptibility of monocyte-derived macrophages to infection. Masihi, K. notes that interleukin 2 increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies. In summation, the art teaches that cytokines can be inherently toxic, have unclear pharmacological behavior and also have pleiotropic effects. Hence, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated.

Additionally, while the art teaches that oligonucleotides containing the CpG motif are capable of stimulating a Th1 type immune response, however, the art also teaches that the Th1 associated cytokine profile for these oligonucleotides vary from one oligonucleotide and species of subject to the next, as evidenced by Krieg et al. [10] and Mutwiri et al. [11] Krieg et al notes that each oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies. Krieg et al. particularly notes that the type of cytokine stimulated by oligonucleotides containing the CpG motif is distinct from one oligonucleotide to the next. Additionally, both Krieg et al. and Mutwiri et al. note that the level and type of immune stimulation varies depending on i) the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif; ii) the spacings

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[9] Masihi, K. Fighting infection using immunomodulatory agents. Expert Opin. Biol. Ther., 2001, Vol. 1, No. 4, 641-653. [Lines 15-25, left column of page 646, in particular]

[10] Krieg et al., CpG motif in bacterial DNA and their immune effects. Annu. Rev. Immunol., 2002, Vol. 20, 709-760. [paragraph that bridge pages 716-717, in particular.]

between CpG motifs; iii) the numbers of CpG motifs in an oligonucleotide; iv) the absence or presence of a CpG motif to the end of the oligonucleotide; and v) the context in which the CpG motif is presented in the sequence.

The CpG art further teaches that the immunostimulatory activity of oligonucleotides containing the CpG is very species specific, as evidenced by Mutwiri et al. Table 1 of Mutwiri et al. provides that the *in vitro* immunostimulatory activity of oligonucleotides containing the CpG motif varies from one species to the next. Mutwiri et al. also notes that the level of immunostimulating induced by a particular oligonucleotide is also dependent on the sequence(s) flanking the CpG motif. Specifically, Mutwiri et al. notes that the GTCGTT motif, which is the optimal motif for humans, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens; whereas the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice.

Furthermore, both Krieg et al. and Mutwiri et al. sets forth that the recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 associated cytokines. However, Mutwiri et al. provides that TLR-9 has only been identified in mice and humans. Mutwiri et al. also provides that the TLR-9 is differentially expressed in humans and mice. Hence, if the recognition of the CpG motif were dependent of TLR-9, then it would logically follows that the extent of the Th1 type immune response induced by the oligonucleotide would necessarily vary from one

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[11] Mutwiri et al. Biological activity of immunostimulatory CpG DNA motifs in domestic animals. Veterinary Immunology and Immunopathology, 2003, Vol. 91, 89-103. [See 2nd and 3rd full paragraphs, left column of page 93; last sentence of paragraph bridging pages 89-90.]

species to the next. Mutwiri et al. also sets forth that *in vitro* observations do not accurately predict what happens *in vivo*.

Moreover, the potential use of oligonucleotides containing the CpG motif to stimulate a Th1 type immune response that treats and prevents infection is widely speculated in the art. However, efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protect a host from infectious pathogen has proven to be challenging and elusive, as evidenced by Yamamoto et al., [12] Equils et al.,[13] Agrawal et al.,[14] and Olbrich et al.[15] Yamamoto et al. reports that oligonucleotides containing the CpG motif failed to improve the survival in mice challenged with influenza. Equils et al. teaches that such oligonucleotides can induce the HIV transcriptional regulatory elements in long terminal repeats, increasing viral replication. Agrawal et al. teaches that HIV-infected humans treated with oligonucleotides containing the CpG motif showed dose-dependent increases viral load. Lastly, Olbrich et al. teaches that the administration of oligonucleotides containing the CpG motif accelerated and increased the severity of Friend retrovirus in mice. In the case of Olbrich et al., the author notes that the use of oligonucleotides containing the CpG motif for the treatment of viral infection may be a double edge sword that can resolute in effective therapy but also in acceleration of

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[12] Yamamoto et al., Oligodeoxyribonucleotides with 5'ACGT-3' or 5TCGA-3 sequence induce production of interferons. Curr. Top. Microbiol. Immunol. 2000, Vol. 247, 23-40.
[13] Equils et al. Toll-like receptor 2 (TLR2) and TLR9 signaling resulted from HIV-long terminal repeat transactivation and HIV replication in HIV-1 transgenic mouse spleen cells: implications of simultaneous activation of TLRs on HIV replication. J. Immunol. 2003, 170, 5159-5164.
[14] Agrawal, et al. Was induction of HIV1 through TLR9? J. Immunol. 2003, 171, 1621-1621.
[15] Olbrich et al. Preinfection treatment of resistant mice with CpG oligodeoxynucleotides renders them susceptible to friend retrovirus-induced leukemia. J. Virol., 2003, 77, 10658-10662.

disease. Olbrich et al. notes that this double edge sword observation may be dependent on the time point of treatment.

Hence, overall, the literature notes the use of CpG to stimulate the production of cytokines, the use of cytokines to influence viral infection, and the development of a treatment regimen for diseases is unpredictable and complicated.

Predictability or unpredictability of the art:

As discussed above, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated. The art also recognizes that use of CpG to stimulate cytokine production, the use of the induced cytokine to influence viral infection, and the development of treatment regimen unpredictable and complicated. The art additionally teaches that the efforts to harness the immunostimulatory activity of oligonucleotides containing the CpG motif to trigger an innate immune response that protects a host from infectious pathogen has proven to be challenging and elusive.

Quantity of experimentation necessary:

Extreme undue burden of experimentation would be imposed upon the skilled artisan practicing the claimed invention. As stated above, Applicant has not provided much, if any, guidance or direction relating to the claimed invention. All that Applicant has provided is a conclusion that is made on the basis of generalized concepts that CpG oligonucleotides are capable of inducing a biased Th1 immune response, and that Th1 immune response are useful in treating infections. And the formation of a conclusion based on generalized concepts renders the conclusion flawed. Generalized concepts are directed to support a general direction of studies or research; however,

they do not support concrete conclusions, the use of oligonucleotides to treat HBV. Concrete conclusions must be substantiated by facts, including evidence. In the instant case, while the general direction of research may be outlined for the skilled artisan, the skilled artisan would not readily be able to practice the claimed invention without the burden of undue experimentation. The path the skilled artisan must take in his research is marked with many challenges that are recognized in the art, including the complex nature of oligonucleotides containing CpG motif and the complexity of the immune system, including the Th1 type immune response and the functional characteristics of its associated cytokines. Hence, in view of the lack of any guidance in the specification concerning the effective use of oligonucleotides to treat, prevent or ameliorate viral infection in a subject; the unpredictability of oligonucleotides containing CpG motif to stimulate specific immune response; and the inherent toxicity, the unclear pharmacological behavior, and the pleiotropic effects of cytokines; the skilled artisan would not be able to reasonably practice the claimed invention without an undue burden experimentation. Thus, the claims are rejected under 35 U.S.C § 112, 1st paragraph for failing to comply with the enablement requirement.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

Double Patenting

6. In response to the double patenting rejection issued, Applicant elects to defer substantive rebuttal until allowable subject matter is indicated.

Applicant's submission has been considered, however, until the rejections are properly addressed, the rejections are maintained for the reason(s) set forth in the record.

Additionally, the provisional rejection over claim(s) of copending patent application no. 10/613524 is withdrawn in view of Applicant's submission.

7. As previously presented, the nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. In response to the provisional double patenting rejection, Applicant has deferred substantive rebuttal until the claimed invention is allowed.

Applicant's request has been noted, however, until the rejections are properly addressed, the rejections are maintained. It should be noted that the provisional double patenting rejections of the claims over claims of copending Application Nos. 10/613524 and 11/071836 are withdrawn.

9. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70, 72-86 and 97-102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 59-61, of copending Application No. 11/255100.

The claimed invention is directed to a method of treating, preventing and ameliorating hepatitis B viral infection with the administration of an oligonucleotide comprising the CpG motif.

Claims 59-61 of the conflicting patent application is directed to a method of treating hepatitis B viral infection with the administration of an oligonucleotide

comprising the CpG motif, SEQ ID NO: 27, to a subject having or at risk of HBV infection.

The difference between the claims is: claims 59-61 of the conflicting patent application is directed to the administration of a specific oligonucleotide. However, the claimed invention recites the transitional term "comprising". Hence, the claimed invention also encompasses the species of oligonucleotides recited in the claims of the conflicting patent application. In the instant, the species of oligonucleotides recited in claims 59-61 of the conflicting patent application is encompassed by the genus of oligonucleotides recited in the claims of the instant patent application. Thus, the species of oligonucleotides recited in claims 59-61 of the conflicting patent application anticipates the genus of oligonucleotides recited in the claims of the instant patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Claims 50, 52-53, 55-57, 59-60, 62-64, 66-70, 72-86 and 97-102 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-33, of copending Application No. 10/987146.

Claims 19-33 of the conflicting patent application is directed at a method for treating viral infection with the administration of an oligonucleotide comprising the CpG motif to said subject.

The difference between the claim sets is: the conflicting patent application is not limiting to the type of viral infection it intends to treat. However, in view of the disclosure

of the conflicting patent application, by viral infection, Applicant intends to encompass hepatitis B viral infections. See line 19, page 13 of the conflicting patent application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Note: Some of the rejections stated above, in part, based on the specification of a previously issued patent, rather than the claims. In support of the use of this material, the examiner notes the following excerpt from MPEP section 804 II(B)(1):

> When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. This does not mean that one is precluded from all use of the patent disclosure.

The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. In re Boylan, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in

contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Thus, the courts have held that it is permissible to use the specification in determining what is included in, and obvious from, the invention defined by the claim on which the rejection is based. This is true even where elements are drawn from the specification describing the claimed invention which are not elements in the claim itself.

Conclusion

11. No claims are allowed.

12. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Emily Le/
Patent Examiner, Art Unit 1648

/E. L./